Review Article

Challenges and unanswered questions for the next decade of immune-oncology research in NSCLC

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Abstract: Over the last 20 years there have been great advances in the treatment of lung cancer. Immune checkpoint blockade together with targeted therapies have provided oncologists with the means to improve survival of non-small cell lung cancer (NSCLC) and patients with a better quality of life and therapies with manageable toxicity. Maybe in a short period of time the possibility of a cure in metastatic NSCLC will be raised. Therefore, continued research into new drugs, biomarkers and especially combination therapies is necessary in order to expand the clinical benefit of the current treatments to a broader population of NSCLC patients. The purpose of our review is to highlight our thoughts about potential mechanisms of resistance to immunotherapy that, if better explored, can provide us with both biomarkers to predict response to these therapies and partners to combine with and prolong the benefit of immune checkpoint blockade. We are presenting our own experience of immunotherapy with a case report from our institution.

Keywords: Lung cancer; immunotherapy; biomarkers; combinations

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Introduction

The concept of cancer immunotherapy is not new, it goes back to 1891 but it was not successful until recently, when the existence and role of immune checkpoints for cancer were understood (1). The role of immune checkpoints like programmed cell death protein-1 (PD-1) or cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is to reduce autoimmune responses against self-tissues. The immune checkpoint PD-1, expressed on $CD8^+$ and $CD4^+$ T cells and B cells, was discovered in 1992 by Japanese investigators (2-4). Almost 10 years later, the same group of investigators discovered the ligands PD-L1 (5) and PD-L2 (6). Both are type I transmembrane proteins. PD-L1 is expressed in lymphoid and non-lymphoid tissues, including various tumor cells and virus-infected cells, while PD-L2 is expressed only on antigen-presenting cells, like dendritic cells and macrophages (7,8). Nivolumab (also known as ONO4538, MDX-1106 or BMS-936558) is the first fully humanized anti-PD-1 monoclonal antibody, developed in 2005, using genetically modified mice carrying loci encoding human immunoglobulins (9).

From 2005 until now, several anti-PD-1 or anti-PD-L1 monoclonal antibodies have demonstrated activity in non-small cell lung cancer (NSCLC) patients alone, or in combination with other anti-tumor therapies in advanced and more recently in early stage disease (10). The anti-PD-1 antibody nivolumab (11) and the anti-PD-L1

antibody atezolizumab (12,13) are approved for the second-line therapy of advanced stage NSCLC, with no biomarker required for the selection of patients. The anti PD-1 antibody pembrolizumab is approved in the same setting, but only when there is a PD-L1 tumor proportion score of at least 1%. Nivolumab failed in the first-line setting in the CheckMate-026 trial (14) while pembrolizumab secured first-line approval on the basis of the Keynote-021 data (15) for PD-L1 positive patients (tumor proportion score of at least 50%).

All mentioned compounds have also been tested in other tumors (16) and have obtained approval in different settings, as shown in *Figure 1*. The last 2 years combination studies with chemotherapy or small molecules have come across the board, with both pembrolizumab and nivolumab being the most widely combined anti-PD-1 agents (17). Pembrolizumab in combination with carboplatin and pemetrexed is approved for the first-line therapy of unselected advanced stage lung adenocarcinoma patients (18,19) (*Figure 1*). Anti-PD-L1 antibodies like durvalumab and avelumab (20) have demonstrated efficacy in lung and other types of tumors and new compounds like BGB-A317, LY3300054, CX-072, PDR001 and FAZ053 have made their entrance in immune-oncology.

Despite the significant survival benefit of immune checkpoint inhibitors for some patients with advanced NSCLC, overall, the objective response rate is not more than 20–30% with a large proportion of patients not responding at all to these therapies (16). Still, we are not in a position to select with confidence the patients to treat with immunotherapy. PD-L1 status guides the first-line therapy but this is not the case for the second-line setting (21). A new pattern of progression, named "hyper-progression" has been described for a small but still significant proportion of patients who progress or die within the first 3 months of therapy with immune checkpoint inhibitors (22). The survival benefit of immune checkpoint inhibitors, at least as monotherapy, has not been confirmed in oncogene-addicted tumors, like, for instance, lung adenocarcinomas carrying epidermal growth factor receptor (EGFR) mutations (23).

In this review we will go through signaling pathways that can provide us with biomarkers for response to immunotherapy and can also be relevant for resistance to immune checkpoint blockade therapy. Potential solutions will be commented. The revision of second and third generation drugs for immuno-oncology is out of the scope of our review. Some thoughts about immunotherapy in early stage NSCLC will be provided.

Biomarkers for immunotherapy: the present

PD-L1 expression is the only accepted biomarker to select patients for immunotherapy but still its performance in discriminating responders from non-responders is debatable. Three immunohistochemistry staining assays are most commonly used (the Ventana SP263, Dako 22C3 and Dako 28-8) (1,24). Caution should be taken with the use of PD-L1 protein expression as an exclusive predictive biomarker, considering the variability of its expression at different sites of disease or at different time points during the treatment course (1,10).

Tumor mutation burden (TMB) is another biomarker of response to immunotherapy across multiple tumor types (25). For instance, although overall the CheckMate-026 was a negative trial, in an exploratory biomarker analysis of TMB by whole-exome sequencing, patients with 243 or more mutations (high TMB) had a higher response rate and a longer progression-free survival with nivolumab in comparison with first-line chemotherapy (14). High TMB can similarly predict efficacy to nivolumab plus ipilimumab in small-cell lung cancer patients, upon progression to first-line therapy (26). Until recently, TMB was assessed only by whole-exome sequencing (14,27), which makes its clinical application complex. Today, targeted next generation sequencing can also be applied to TMB evaluation as a predictor of benefit for immune checkpoint blockade (28). In the recent study of Rizvi *et al.*, targeted next generation sequencing was performed using the Memorial Sloan Kettering Cancer Center-Integrated Mutation Profiling of Actionable Cancer Targets (MSKCC-IMPACT) platform (28). TMB can also be performed using other commercial platforms in both tissue and blood (29). In a retrospective analysis of the CheckMate-012, which evaluated the safety and efficacy of nivolumab plus ipilimumab in the first-line setting of NSCLC patients, TMB as assessed by three methods, whole-exome sequencing, the MSKCC-IMPACT platform and the FoundationOne platform, had similar predictive fidelity for efficacy (30). The cutoff for defining low and high TMB with the FoundationOne panel has been explored in the CheckMate-568 study. A TMB of 10 mutations per megabase was able to discriminate responders from non-responders to the combination of nivolumab plus ipilimumab as presented by Dr. Ramalingam, in the last American Association of Cancer Research meeting (AACR, 2018). For patients with high TMB (>10 mutations per megabase) the combination of nivolumab plus ipilimumab

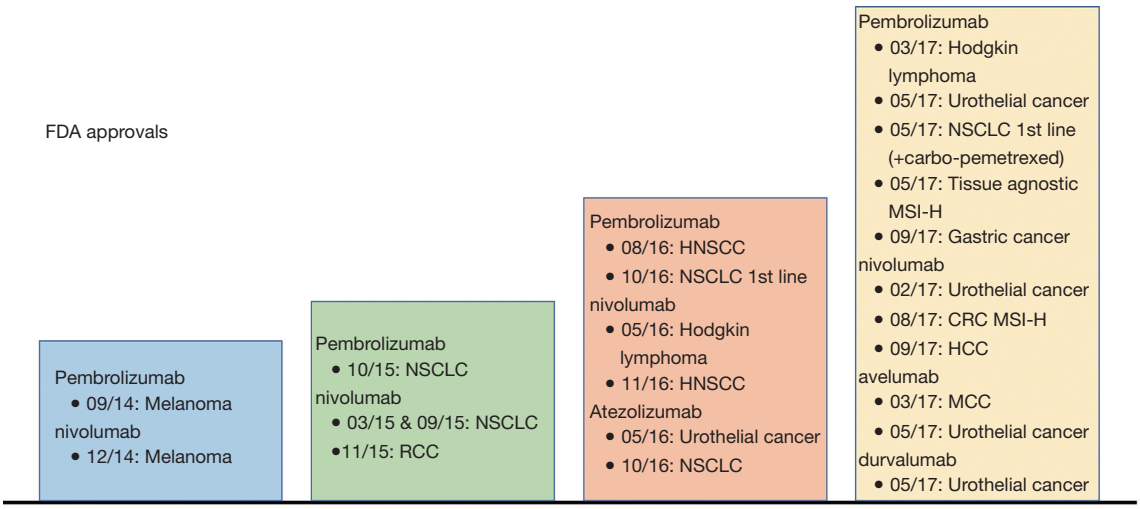


Figure 1 FDA approvals for anti-PD-1 and anti-PD-L1 inhibitors in cancer. FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; MSI-H, microsatellite instability-high; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; MCC, Merkel cell carcinoma.

significantly improved the progression-free survival of treatment-naïve metastatic NSCLC patients in comparison with platinum-based chemotherapy (31). With the GUARDANT360 liquid biopsy test, the detection of six or more variants or more than three variants of unknown significance was found to be predictive of response to immunotherapy (32). In addition, with the same test it has been demonstrated that cell-free DNA velocity is an early surrogate of immunotherapy response (33,34). With the FoundationAct 396 gene-based liquid biopsy test, a blood TMB of more or equal than 16 was found to be predictive of response to atezolizumab (35). Next generation sequencing platforms are also determining microsatellite instability (MSI) status (36). Pembrolizumab is approved for treatment-refractory MSI-high or mismatch repair deficient metastatic solid tumors (37,38) (*Figure 1*).

PD-L1 expression, TMB and MSI are means to select immunotherapy for cancer patients including NSCLC. In most of the studies, no association has been found among them, resulting in a difficult decision-making process, especially in the second-line therapy of NSCLC. Another challenging question in immunology is how the immune system affects cancer development and progression. The immune system can recognize and kill tumor cells but it can also facilitate tumor progression by establishing a tumor microenvironment that accommodates tumor growth (cancer-immune editing) (39).

Novel biomarkers for immunotherapy and potential combinations: the future

PD-L1 expression is induced by oncogenic signals or by inflammatory cytokines such as interferon-γ. We reported interferon-γ as a biomarker to predict response to immune checkpoint blockade in melanoma and NSCLC patients receiving nivolumab and pembrolizumab, respectively (40). Indeed, now interferon-γ signatures are prospectively validated as a biomarker in ongoing immunotherapy clinical trials (40). In the absence of interferon-γ in the tumor microenvironment, CKLF-like MARVEL transmembrane domain containing protein 6 and 4 (CMTM6 and CMTM4) are the only regulators of PD-L1 expression (41). CMTM6 is a transmembrane protein that associates with PD-L1 in the cell surface and protects it from lysosomal degradation (42) (*Figure 2*). For this function CMTM6 cooperates with its closest family member, CMTM4, but not with other CMTM family members (42). A CMTM6/4 inhibitor is in clinical development (*Table 1*).

In surgical resected NSCLC specimens, PD-1 (or B7-H1) is co-expressed with B7-H3 and both molecules repress the antitumor immune response by inhibiting T cell infiltration and IFN-γ secretion (57) (*Figure 2*). The negative prognostic significance of B7-H3 expression is more evident in smokers and EGFR wild type lung adenocarcinoma patients (58). Combining blockades of B7-H3 and PD-1 enhanced therapeutic tumor control

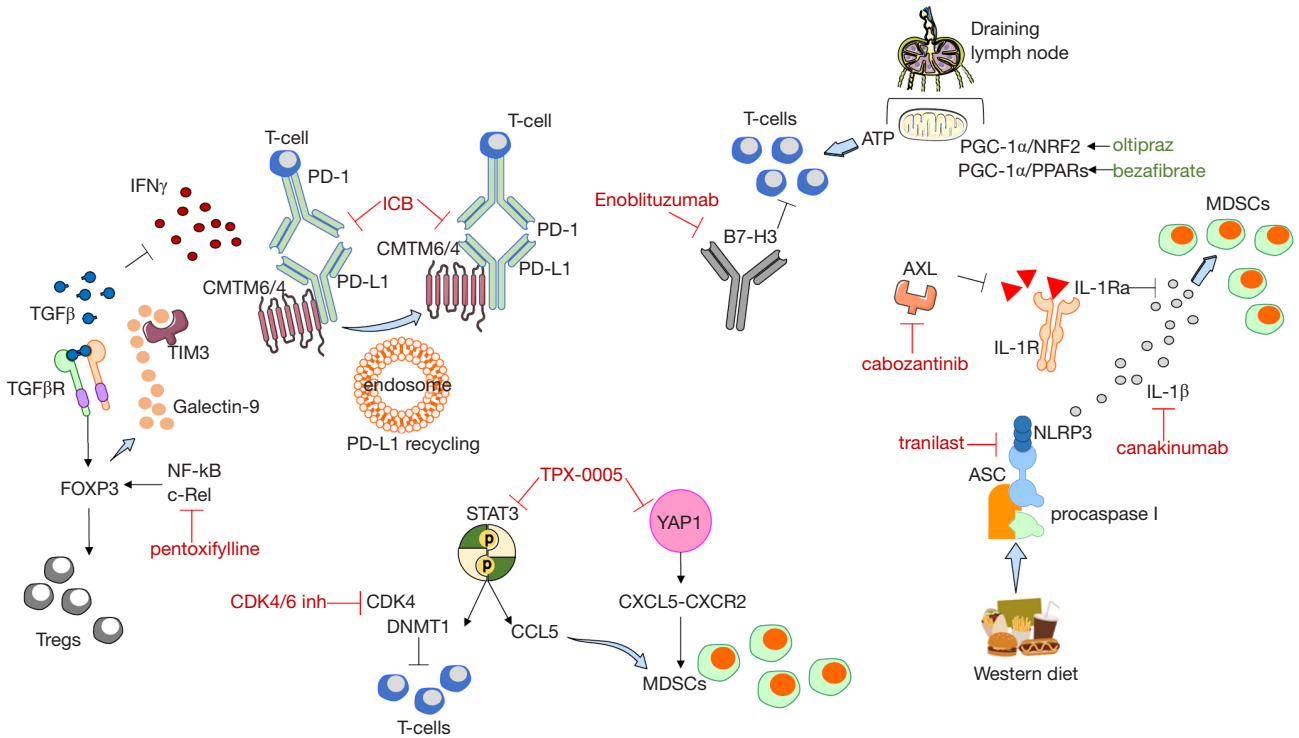


Figure 2 Potential targets to enhance the efficacy of immune checkpoint blockade. Signaling pathways that are related with resistance to anti-PD-1 and anti-PD-L1 therapies and drugs that can be used to abrogate them. ICB, immune checkpoint blockade.

compared to PD-1 inhibition alone, *in vivo* (59,60). A B7-H3 inhibitor, enoblituzumab has shown promising data in a phase I clinical trial and now is being evaluated in combination with anti-PD-1 therapies (ClinicalTrials.gov identifier NCT02475213) (43,44) (*Table 1*).

Whether or not there is a positive correlation between EGFR mutations or anaplastic lymphoma tyrosine kinase (ALK) rearrangements and PD-L1 expression is not clear. Several studies have shown that the expression of PD-L1 is higher in EGFR or ALK altered NSCLC in comparison with wild type tumors (61-66) but it is not related with better response to immune checkpoint blockade. Still there are few studies showing decreased expression of PD-L1 in EGFR or ALK driven tumors (67,68). We found that patients with high PD-L1 expression have better outcome to EGFR tyrosine kinase inhibitors (TKI) (69). Co-expression of transcriptional regulators, like signal transducer and activator of transcription 3 (STAT3) and yes-associated protein 1 (YAP1) (70) and receptor and non-receptor tyrosine kinases (RTKs and non-RTKs), mainly AXL and CUB domain-containing protein 1 (CDCP1) (45) are related to worse outcome to EGFR TKIs. This can also partially explain the lack of response of EGFR mutant NSCLC to immune checkpoint inhibitors. Both STAT3 and Src-YAP1 have an immunosuppressive role by either interfering with interferon responses or by inducing the expression of chemokines that attract myeloid-derived suppressor cells (MDSCs) (71). YAP1 plays a key role in the efficient recruitment of MDSCs through activation of the CXCL5-CXCR2 axis (72). In our study, the multi-kinase inhibitor TPX-0005 was able to reverse the EGFR TKI-induced activation of STAT3, Src-YAP1 and RTKs (45) The combination of TPX-0005 with immune checkpoint blockade can be of interest in EGFR mutant NSCLC or other types of tumors (*Table 1*). After many studies having shown the negative impact of immune checkpoint inhibitors as second line therapy in EGFR or ALK positive NSCLC (73), for the first time, an immunotherapy combinatorial approach, specifically atezolizumab, bevacizumab carboplatin-paclitaxel, demonstrated clinically meaningful progression-free survival benefit in the first-line setting of patients with EGFR or ALK rearrangements (74). Still, whether this complex combinatorial approach will have a clinical impact in the first-line therapy of EGFR or

Table 1 Combinations of immune checkpoint blockade (ICB) and targeted therapies that merit to be investigated

ICB+	Mechanism	Drugs available	Already ongoing studies	Ref
CMTM6/4 inhibitor	Decrease PD-L1 stability	E11889 (in development)	–	(41,42)
BH-73 inhibitor	Increase of: ❖ T cell infiltration ❖ IFN-γ secretion	Enoblituzumab	NCT02475213	(43,44)
STAT3, Src-YAP1 inhibitor	Inhibition of: ❖ RANTES (CCL5) ❖ DNMT1 ❖ CXCL5-CXCR2 axis	TPX-0005	–	(45)
CDK4/6 inhibitor	DNMT1 suppression	Abemaciclib, palbociclib, ribociclib, trilaciclib	NCT02791334 NCT02079636 NCT02779751	(46,47)
AXL inhibitor	Interleukin-1 receptor antagonist upregulation	Cabozantinib	–	(48)
IL-1β inhibitor	Suppression of: ❖ MDSC recruitment ❖ NLRP3 inflammasome	Canakinumab, tranilast	NCT02900664	(49,50)
TGFβ inhibitor	Inhibition of: ❖ FOXP3 ❖ CTLA4 ❖ Galectin 9 ❖ TIM3	M7824	NCT03436563 NCT03427411 NCT02517398 NCT03315871	(51-54)
c-Rel inhibitor	Inhibition of FOXP3	Pentoxifylline	–	(55)
PGC-1α activator	Mitochondrial activation	Oltipraz, bezafibrate	–	(56)

ALK positive NSCLC patients is doubtful.

CC chemokine ligand 5 (CCL5), also known as RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted), is a transcriptional target of STAT3 and is related to immune suppression and, ultimately, resistance to immunotherapy (75,76). Among other chemokines, RANTES is important for trafficking MDSCs and regulatory T cells (Tregs) to the tumor (75). Other studies have related RANTES with the recruitment of $CD8^+$ cells and therefore response to immune checkpoint blockade (77,78). This is probably due to the fact that RANTES attracts a wide range of immune cells and its effect may be differentiated according to the tumor type or even according to the experimental procedures (e.g., *in vitro* or *in vivo* studies). STAT3 activates DNA methyltransferase 1 (DNMT1) that impairs T-helper 1 cytokine production and responsiveness to checkpoint blockade (79,80) (*Figure 2*). Cyclin-dependent kinase 4 (CDK4) interacts with DNMT1 and the combination of immune checkpoint inhibitors with CDK4/6 inhibitors was found to be synergistic *in vitro* and *in vivo* (46,47) (*Figure 2*). Clinical trials are now ongoing with this combination (ClinicalTrials.gov identifiers NCT02791334, NCT02079636, and NCT02779751) and could be of important benefit for tumors with poor outcomes to current immunotherapies like EGFR mutant NSCLC.

On the other hand, AXL matters for tumors that do not derive benefit from immune checkpoint blockade, like prostate cancer (81). AXL and other mesenchymal transition genes are related with innate resistance to anti-PD-1 therapy (82). In mice models of castration-resistant prostate cancer, immunotherapy alone induced the AXL expression and only when a combination of immunotherapy with cabozantinib (MET, VEGFR2, AXL and RET inhibitor) was administered, RTKs, including AXL, were downregulated, while interleukin-1 receptor antagonist (IL-1Ra) was upregulated (48). IL-1Ra suppresses MDSC recruitment (83) (*Figure 2*). IL-1Ra is a regulator of IL-1β signaling. Canakinumab, an anti-inflammatory therapy for atherosclerotic disease, is a human anti-IL-1β monoclonal

antibody (84). IL-1β inhibition with canakinumab therapy is also related to reduction in lung cancer mortality and reduction in lung cancer cases in patients with previous heart attack and inflammatory atherosclerosis (49). A study with the combination of the anti PD-1 antibody spartalizumab (PDR001) with canakinumab is ongoing (ClinicalTrials.gov identifiers NCT02900664).

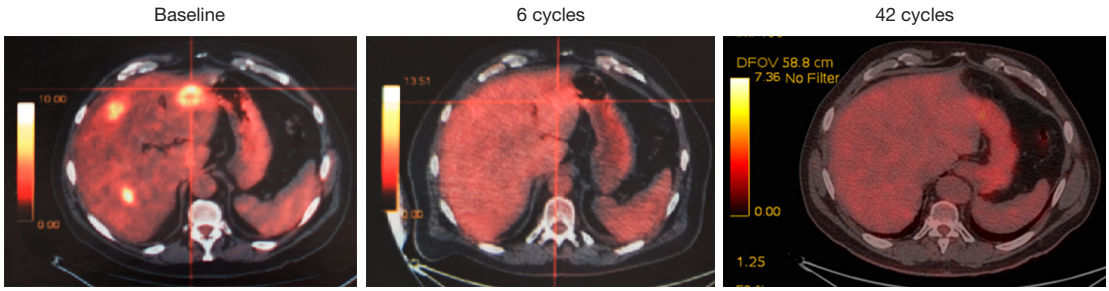
Host-related influences may be responsible for the heterogeneous responses and failures during immune checkpoint blockade therapies. A strong interrelationship has been described between the host microbiota and immunotherapy (85). Inflammasome is an innate immune pathway, responsible for the production of the inflammatory cytokine IL-1β (*Figure 2*). In response to danger signals like bacterial or viral infections or inflammatory diseases, NOD-like receptors (NLR) interact with adaptor molecule apoptosis-associated speck-like protein (ASC) and procaspase I to form the inflammasome (86). NLRP3 inflammasome is the best characterized inflammasome. There is evidence that NLRP3 activation inhibits antitumor immune response by augmenting the function of immunosuppressive cells like MDSCs (87) (*Figure 2*). Western diet triggers NLRP3 innate immune reprogramming, which may also explain the clinical benefit of canakinumab in humans with cardiovascular risk (49,84,88). Tranilast, an old anti-allergic clinical drug, is a direct NLRP3 inhibitor (50) (*Table 1*).

Transforming growth factor-β (TGFβ) signaling is related to immunosuppression and restriction of T-cell infiltration. TGFβ reduces the expression of interferon-γ, attenuates the activity of $CD8^+$ T cells and, more importantly, induces the expression of the transcription factor Forkhead box P3 (FOXP3) (*Figure 2*). FOXP3, among other functions, is responsible for the differentiation of Tregs and the maintenance of their signaling. Furthermore, the TGFβ-FOXP3 axis stimulates the expression of CTLA-4 and galectin 9, the ligand of the immune-inhibitory receptor T-cell immunoglobulin domain and mucin domain-3 (TIM-3) (51) (*Figure 2*). The combination of anti-PD-1/PD-L1 antibodies with drugs that block TGFβ was highly synergistic in microsatellite-stable colon (52) and urothelial (53) cancer and enabled immune infiltration. M7824, a bifunctional fusion protein targeting PD-L1 and TGF-β, is now in clinical trials (ClinicalTrials.gov identifiers NCT03436563, NCT03427411, NCT02517398 and NCT03315871) (54). FOXP3 and Tregs development is also dependent on c-Rel, a subunit of the canonical nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway (55) (*Figure 2*). Pentoxifylline is an FDA-approved drug, already in the market, used in patients to increase blood flow in the hands and feet of people with poor circulation. It also causes c-Rel degradation and impairs Treg identity (55). Of course, caution should be taken since the destruction of Tregs can generate autoimmune reactions.

Immunotherapy for early stage NSCLC: adjuvant or neoadjuvant?

Immunotherapy in lung cancer has demonstrated significant activity in early stage disease (89). When Rafael Rosell was asked about the PACIFIC study, he commented that the results undeniably point to implementing immunotherapy with chemoradiotherapy in patients with stage III NSCLC. In addition, he said that the study prompts us to gain further insights on the immune effects of irradiation (90). Surprisingly, two administrations of nivolumab before surgical resection of stage I–IIIA NSCLC was associated with a major pathological response in 45% of resected tumors (91). Whether the effect of immunotherapy can be stronger in the neoadjuvant setting compared to after dissection of lymph nodes, which can reduce the anti-tumor activity of the immune system, merits further investigation in lung cancer (56,92). In breast cancer mice models, neoadjuvant immunotherapy had a significant better therapeutic efficacy in comparison with adjuvant therapy (93).

The rapid proliferation and differentiation of T cells is necessary for an effective PD-1 blockade therapy. Immune metabolism requires mitochondria in draining lymph nodes to supply tumor-reactive cytotoxic T lymphocytes with ATP, but the preexisting cytotoxic T lymphocytes are not enough for durable tumor-growth inhibition. Indeed, draining lymph node ablation cancels the efficacy of the PD-1 blockade therapy (56). PPAR-gamma coactivator 1α (PGC-1α) enhances mitochondrial activity through partner transcription factors: nuclear respiratory factors (NRFs) and peroxisome proliferator-activated receptors (PPARs) (56). Oltipraz and bezafibrate are small-molecule activators of PGC-1α /NRF2 and PGC-1α/PPARs, respectively, and have demonstrated synergistic tumor suppression activity with anti-PD-L1 monoclonal antibodies in animal models (56).



PET CT (SUV)	LUNG	LIVER	T12	4th right rib
21/4/16 basal	6.7	14.6	8.1	10.9
11/8/16 6 cycles	4	--	4.6	2.9
3/11/16 12 cycles	2	--	2.1	1.9
3/2/17 18 cycles	1.9	--	1.8	1.5
7/4/17 22 cycles	1.7	--	--	--
20/10/17 30 cycles	2	--	--	--
20/1/18 42 cycles	2	--	--	--

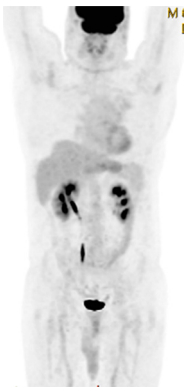


Figure 3 Long-term survival of a patient with metastatic squamous cell NSCLC treated with second-line nivolumab. Upper part: metastatic localizations in the liver in the PET-CT-scan of April 2016 (on the left), before treatment with nivolumab, August 2016, after 6 cycles of treatment with nivolumab (on the middle), and January 2018, after 42 cycles of treatment with nivolumab (on the right). Lower part: the table on the left shows the metabolic activity of the disease during the treatment. The whole-body PET study (on the right) is of January 2018, after 42 cycles of treatment with nivolumab. SUV, standardized uptake value; T12, twelfth thoracic vertebra.

Our experience and future perspectives

Immunotherapy constitutes a milestone in the advancement of lung cancer treatment. Until now, we could never consider that a 16% 5-year overall survival rate could occur in heavily pretreated metastatic NSCLC patients (94). We report the case of a 62-year-old male patient who arrived to our institution in April 2016, with a metastatic squamous cell carcinoma of the lung and progression to first-line therapy. The patient was initially diagnosed in October, 2015, with a squamous cell carcinoma of the lung and brain metastases. He was treated in his local hospital with four cycles of cisplatin with paclitaxel, consolidation radiotherapy of the lung and the mediastinum and radiosurgery of the brain metastases. Only three months after the end of the treatment, he progressed with new liver and bone metastases. At that time the patient came to us with a performance status of 2 for a second opinion. We initiated second-line therapy with nivolumab 3 mg/kg every 2 weeks. There was no tissue available for molecular analysis and we planned to perform a biopsy of the liver metastases if the performance status of the patient improved with the treatment. An impressive clinical, radiographic and metabolic response, with complete disappearance of the liver metastases was observed after only 6 administrations of nivolumab. The patient is still radiographically free of disease (after 42 cycles), 2 years and 6 months after being diagnosed with metastatic NSCLC. We never had the opportunity to perform a rebiopsy. The patient continues therapy with nivolumab without any significant toxicity (*Figure 3*). Immune related toxicities are out of the scope of our review, but there are several reports and guidelines that are useful for oncologists and hospitalists who are treating patients receiving immune checkpoint inhibitors (95,96).

In the first-line setting of NSCLC patients without driver genetic alterations, treatment decisions have become more complex than in the past. The results of the CheckMate-227 showed that nivolumab plus ipilimumab is an effective treatment option for patients with high TMB. Still, there are several challenges, such as the reliability of the metrics to identify patients with high TMB or the tissue requirements for such analysis that usually surpasses the

quantity of material that we obtain by performing small biopsies. Furthermore, the turnaround time of a targeted next generation sequencing cannot be less than 10 days, the cost of the test is significantly high and it is not easily available in all hospitals. In the CheckMate-227, patients were not randomized by TMB and the overall survival results are relatively immature with a non-significant trend toward improved overall survival for patients with high TMB receiving the immunotherapy combination. On the other hand, we have the results of the Keynote-189 in which the benefit in progression-free and overall survival of pembrolizumab combined with platinum-based chemotherapy extended across all PD-L1 levels, even patients with low PD-L1 expression. Last but not least we should not forget that pembrolizumab alone has comparable efficacy to pembrolizumab combined with platinum-based chemotherapy, has lower risks for side-effects and preserves the option of platinum-based chemotherapy upon disease progression, for patients with high PD-L1 (97).

Finally, many ongoing trials combine anti-PD-1/PD-L1 monoclonal antibodies with chemotherapy, radiotherapy, targeted therapies or other immune checkpoint inhibitors. Looking at the results of the most relevant clinical trials comparing immunotherapy with chemotherapy (11,15), we observe that survival curves separate at later times (98). However, this is not the case for studies in which immunotherapy is combined with other therapies like chemotherapy or radiotherapy (89,99). When 20% of early events were excluded, more significant P values and more pronounced estimates of the treatment effect were theoretically generated (98). This could be due to the fact that the generation of an adaptive immune response in patients with rapidly progressive disease (100) may be difficult without the combination of immune checkpoint blockade with other therapies, at least for a period of time. Whether the best partner for immunotherapy is chemotherapy, radiotherapy, other immune checkpoint inhibitors, or drugs that target compensatory signaling pathways is now under active investigation. In *Table 1* we provide some rational combinations and biomarkers that may become clinically applicable in the near future, while *Figure 2* graphically explains these pathways.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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